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14. ABSTRACT

Although the immediate effectors of cell function are proteins, the absence of a practical high-throughput approach to explore protein activation has resulted in a reliance on genomic studies for biomarker identification. Comprehensive analysis of the genome and transcriptome in cancer does not capture all levels of biological complexity. Protein function is also dependent on posttranslational modifications. Functional proteomic analysis has the potential to effectively characterize ovarian cancer molecular heterogeneity. As new targeted therapeutics become available, predicting appropriate therapies will also be difficult without functional proteomic analysis. The lack of a validated practical, high-throughput functional proteomics platform remains a barrier to the identification and validation of useful ovarian cancer biomarkers. Reverse phase protein arrays (RPPA) offer a novel emerging approach to quantitative profiling of the levels and activation of multiple proteins in ovarian cancer cells and patient samples obstacles to the application of RPPA to the study of human ovarian cancers. In this study, we expanded the number of potential functional biomarkers by validating commercial antibodies for use with RPPA. We also tested 482 ovarian tumors and compared them to the ovarian cell line data.

15. SUBJECT TERMS
None provided.

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Table of Contents

Introduction (from grant)

Although the immediate effectors of cell function are proteins, the absence of a practical high-throughput approach to explore protein activation has resulted in a reliance on genomic studies for biomarker identification. However, comprehensive analysis of the genome and transcriptome in cancer does not capture all levels of biological complexity. Protein function is highly dependent on posttranslational modifications (e.g. phosphorylation). Further, the combinatorial effects of the multiple genomic aberrations in ovarian cancer may be most clearly manifest at the proteomic level. Functional proteomic analysis has the potential to effectively characterize ovarian cancer molecular heterogeneity. As new targeted therapeutics become available, predicting appropriate therapies and potential sites for intervention will also be difficult without functional proteomic analysis. We thus hypothesize that functional proteomics contains a robust information archive that is capable of determining patient prognosis, predicting response to particular therapeutics, establishing biologically relevant dosing and identifying early responders, while allowing triage of non-responders to more effective therapeutics. However, the lack of a validated practical, high-throughput, quantitative functional proteomics platform remains a key challenge and barrier to the identification and validation of useful ovarian cancer biomarkers. Reverse phase protein arrays (RPPA) offer a novel emerging approach to quantitative profiling of the levels and activation of multiple proteins in ovarian cancer cells and patient samples. Our operating hypothesis is that the use of RPPA for identification and validation of biomarkers will facilitate the development of molecularly targeted treatments in specific subsets of ovarian cancer patients. The goals of this study are: 1. to establish the potential utility of RPPA for biomarker identification in ovarian cancer cell lines, and 2. to overcome obstacles to the successful application of RPPA to the study of human ovarian cancers.

Statement of work *(from grant)*

Specific Aim 1 To validate and apply ovarian cancer relevant antibodies to the development of a functional proteomics ovarian cancer cell line resource (0-9 months):
Specific Aim 2 To develop RPPA as a practical tool that can identify and validate biomarkers in patient samples (10-18 months):

Body
Specific Aim 1a: Validate new Antibodies
Using funds from this grant, we have expanded the number of antibodies that are available for our functional proteomics Reverse Phase Protein Arrays. At the start of this project, we had 60 validated antibodies, and by the end we expanded the antibody list to include 123 additional validated antibodies (see Table 1). Additional funds have expanded the list to 148 validated antibodies. In Table1, “use with caution” antibodies are not included as validated but may be used under certain circumstances (low dynamic range, so only with high protein concentration samples will give meaningful data, not single-band specific in some cell types but useful in others or on cell lines, etc.)

Antibodies are considered validated if they pass a set of rigid criteria. Because RPPA is a high throughput dot-blot, all antibodies must be single-band specific. Off-target bands or high backgrounds that can be ignored on Western blots that separate the bands based on size can interfere with the RPPA analysis. The antibodies must also be quantitative; if an antibody has no dynamic range, then it may be a wonderful antibody for immunohistochemistry, but it cannot be used in RPPA to get concentration information from the serial dilutions. The quantitation on RPPA must also correlate with the Western blot concentrations. For validation, we use a minimum cut-off of R-squared 0.6 for the correlation between RPPA and western blotting for each antibody. Figure 1 outlines the methodology used for validation of individual antibodies for RPPA. Overall, 35% of antibodies failed validation. Of these, 33% failed on Western blots due to multiple bands or because the primary band was not of the correct size. An additional 42% passed the Western blot analysis, but failed on RPPA because of high backgrounds or low signal. The other 25% of antibodies failed because of too low a signal correlation between RPPA and Western blotting.

Specific Aim 1b: Test the newly validated antibodies on ovarian cancer cell lines.

We gathered 50 ovarian cell lines to use in a test to validate 183 different antibodies. After Short Tandem Repeat Profiling (STR), we dropped 11 of the cell lines for a total of 37 validated cell lines. Seven cell lines proved to be mixtures of more than one cell line and these samples were not included in the RPPA array. A further six lines were dropped from our original proposal because their STR profiles did not match known profiles or were the same as other known STR profiles (HOC1, HOC7, HOC8 should be from the same patient, but their STR profiles did not match; Ishikawa's STR profile matched an endometrial cell line; A1847 matched OVCAR8; OVCA429 and OVCA433 have the same STR profile). The six lines were retained in the RPPA; for example, the HOC1 and HOC7 cell lines clustered together indicating they came from the same patient, but HOC8 did not. Since there is no reference STR profile for any of the HOC lines, it is hard to draw any conclusions from these lines. Please see the heat map below in Figure 2 showing expression of each protein or phosphoprotein in each cell line.

Specific Aim 1c: Provide information to ovarian community.

Most of cell line information is now available to the scientific community through the Cell Line Encyclopedia (http://www.broadinstitute.org/software/cprg/?q=node/11) and through the Wellcome Trust Sanger Institute (http://cancer.sanger.ac.uk/cancergenome/projects/cell_lines/). We are in the process of developing our own database for the ovarian cancer cell lines which will include the RPPA data generated using funds from this grant, plus mutational data generated for the cell lines. We will also include the copy number information, since many ovarian cancers are driven by insertions/deletion events. This database will allow users with different levels of access so that we will allow public data to be viewed by registered users and private data to be uploaded, viewed and analyzed by restricted users.

Specific Aim 2 To develop RPPA as a practical tool that can identify and validate biomarkers in patient samples (10-18 months):

With the departure of Dr. Bryan Hennessy, I was not able to obtain 20 ovarian samples from the operating room. Instead of 20 samples from the operating room, I have analyzed 482 ovarian samples that were available through the Kleberg Center for Molecular Markers. Also, the original concept of obtaining tissue, then incubating the samples at various time points to see the effect on RPPA –determined protein levels had already been done using breast tissue. The results of those studies indicate that there is little effect on the relative protein concentrations as determined by RPPA, even for phospho-proteins. One possible reason for this is that although Western blots show a great deal of degradation over the course of hours when incubated at room temperature, for RPPA which is a dot-blot, the only species that needs to remain intact is the short epitope recognized by the antibody. Since RPPA uses denatured proteins, and the antibodies that are chosen are selected on denatured proteins, additional degradation has less of an impact on the relative protein concentration than does Western blotting techniques.

Figure 3 shows the heatmap that was generated with one set of the human ovarian samples. Of the 482 samples, 413 were high grade serous ovarian cancers, 2 were Malignant Mixed Mullerian Tumors, 12 were endometriod, 8 were clear cell and the remaining 47 were mixed or not determined. Included in the RPPA experiment were Melanoma and lung tumors, which clustered separately from the ovarian samples in this set.

To confirm that the data generated by RPPA using ovarian tumor samples was biologically relevant, I looked at the clustering of the various antibodies in the tumor samples to determine whether similar antibodies were grouped together. As can be seen in Figure 3, Table 2 and in Table 3, many of the antibodies within a pathway clustered together, and often the antibodies targeting different phosphorylation sites on the same protein clustered next to one another. It can also be seen that "Not Valid" antibodies often fall into random clusters.

We also tested 20 samples in duplicate, to make sure that they clustered together. We show that both with cell lines and with tumor samples, duplicate samples clusters either next to each other or at least are a part of the same cluster.

We also compared the tumor samples to the cell lines, to see if we could find cell lines that associated with groups of tumors. Since the protein concentration was too different between tumor samples and cell lines,

unsupervised hierarchical clustering will group cell lines and tumor samples separately. Instead, we looked at the relative position in the cell lines and the tumors separately. The tumor samples were grouped into a training set of 47 samples, chosen randomly, and a 435 test set with group I being advanced stage and group II being early stage. Exclusion of all non-serous ovarian tumors did not affect the results. The RPPA data was combined with limited mutational information of the samples, along with limited Affymetrix SNP 500 copy number data with the goal of identifying early vs late stage tumors and then classifying these historically used ovarian cell lines. After extracting features from each biomarker feature set, each set of marker-based features was used to feed the back-propagation artificial neural network. The network used was a non-linear classifier trained using the Levenberg-Marquardt algorithm. The Leave-one-out sampling scheme was used to train and test the network. The final sensitivity was 95.7% and specificity was 70%. When run on the 435 ovarian samples, the model had 96.7% sensitivity (356/368 samples) and 55.2% (35/67) specificity. The positive predictive value was 91.7% and the negative predictive value was 74.4%. Clinically, discriminating between early and late stage ovarian cancer does not require complicated statistics, but the use of this model was to assign cell lines into early and late stage.
AS is shown in Table 4, by comparing the RPPA data from the tumors to the RPPA data from the cell lines, we were able to group the cell lines into early stage (IGROV1), with 19 cell lines listed as indeterminate. For the case of PA-1, IOSE 29 and IOSE 80, these cell lines could be classified as early stage when RPPA data was combined with the copy number data. In addition to the ability to assign the cell lines into early and late stage, the data allowed classification into five different groups.

Key Research Accomplishments

- Validated 123 Antibodies
- Tested antibodies on 37 validated ovarian cell lines
- Ran RPPA on 482 ovarian tumor samples
- Produced an algorithm that was used to divide the ovarian cell lines into six different groups, one group that corresponds to early stage ovarian cancers and five sub-groups of high grade serous ovarian cancer

Reportable outcomes

There were no papers, grants or manuscripts that were generated from this work

Conclusions

In this study, we have expanded the list of antibodies that can be used in RPPA on human ovarian tumors. The antibodies that we tested were ones that have already been shown to be important biomarkers in ovarian cancer. As is seen in Table 1, these include many more phosphor-antibodies against key signaling protein as well as antibodies such as Ca19.9 that were identified as ovarian cancer biomarkers.

Cell lines are a powerful tool in testing new drugs and drug combinations in a variety of cancers. Using cell lines, breast cancer is now known to be divided into several different diseases and the treatment that is used is different depending on which biomarker is present. Assigning breast cancer cell lines to a sub-group, even cell lines available before the markers were known, is fairly easy if the cell line has one of the known markers. For ovarian cancer, we do not have as easy a task since we lack the key markers, making it harder to determine if a sub-population of patients might respond to a drug. By breaking high grade serous ovarian cancer down into additional groups, it is possible to see if a drug has a positive effect on a sub-group.

RPPA can also be used to help identify targets within the sub-type. While the list of antibodies chosen for validation in this study was based on their importance in ovarian cancer, the entire list of validated antibodies contains biomarkers chosen based on their importance in other cancers as well. Using RPPA, Carey, et al, showed that TGFbeta signaling was associated with response to chemotherapy (169). Many of the markers in this pathway were included based on their importance in breast cancer, not ovarian.

We have also shown that duplicate samples display very similar protein signatures. In most cases, they cluster next to one another when using unsupervised hierarchical clustering. Although not in this study, we have also tested samples across RPPA slides, to see whether the same sample gives the same results, thus allowing combination of samples between slides. Our control lysates are very reproducible and validated antibodies are

also comparable; however, antibodies that are listed as “use with caution” can give variable results. This might be due to the fact that the relative protein concentration is determined by comparison to all of the proteins on that particular slide; if the samples on a given slide do not have a large dynamic range, that can negatively affect the relative protein concentration obtained. On each slide are control cell line lysates, to correct for local staining effects; we are exploring using these control lysates for additional QC steps.

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Supporting Data

Figure 1 A: Validation of AKT.
Panel A shows the digitized RPPA slide along with a plot of all of the concentrations for all samples. These are used to make a "supercurve" which determines relative protein concentration. **Panel B** shows the RPPA slide. **Panel C** is an enlargement of the RPPA slide to show the serial dilution, **Panel D** is the Western blot, using the some of the same lysates as are used on the RPPA slide. **Panel E** shows the correlation curve between the Western blot and RPPA slide.

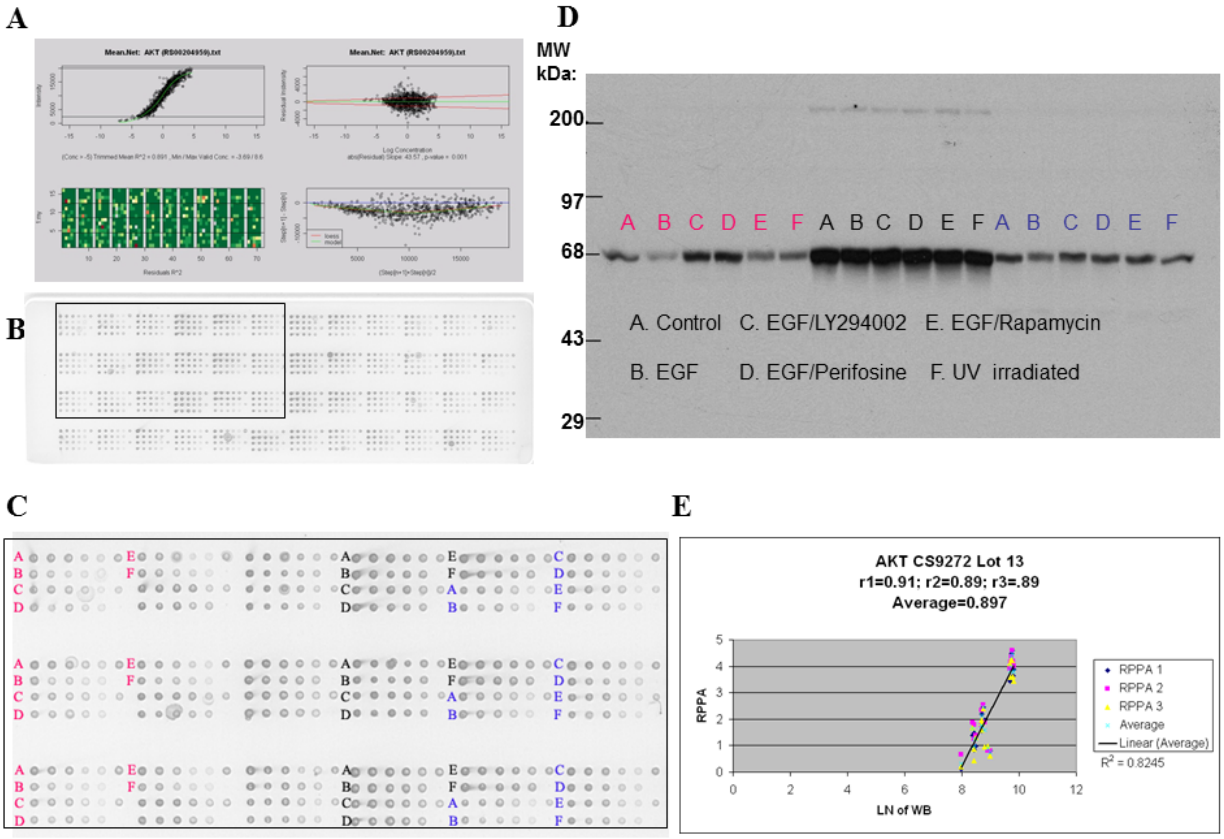

Figure 2: Heatmap of Cell Lines. Shown is the unsupervised hierarchical clustering of all cell line lysates. All cell lines were used, not just ovarian cell lines, as this will allow a broader dynamic range of protein concentrations. The red lines show contributions from ovarian cell lines. In Table 1 is the relative position of all antibodies used, and the numbers are written in different colors indicating that they are clustered together. In this heatmap, red indicates a higher protein concentration and green is lower.

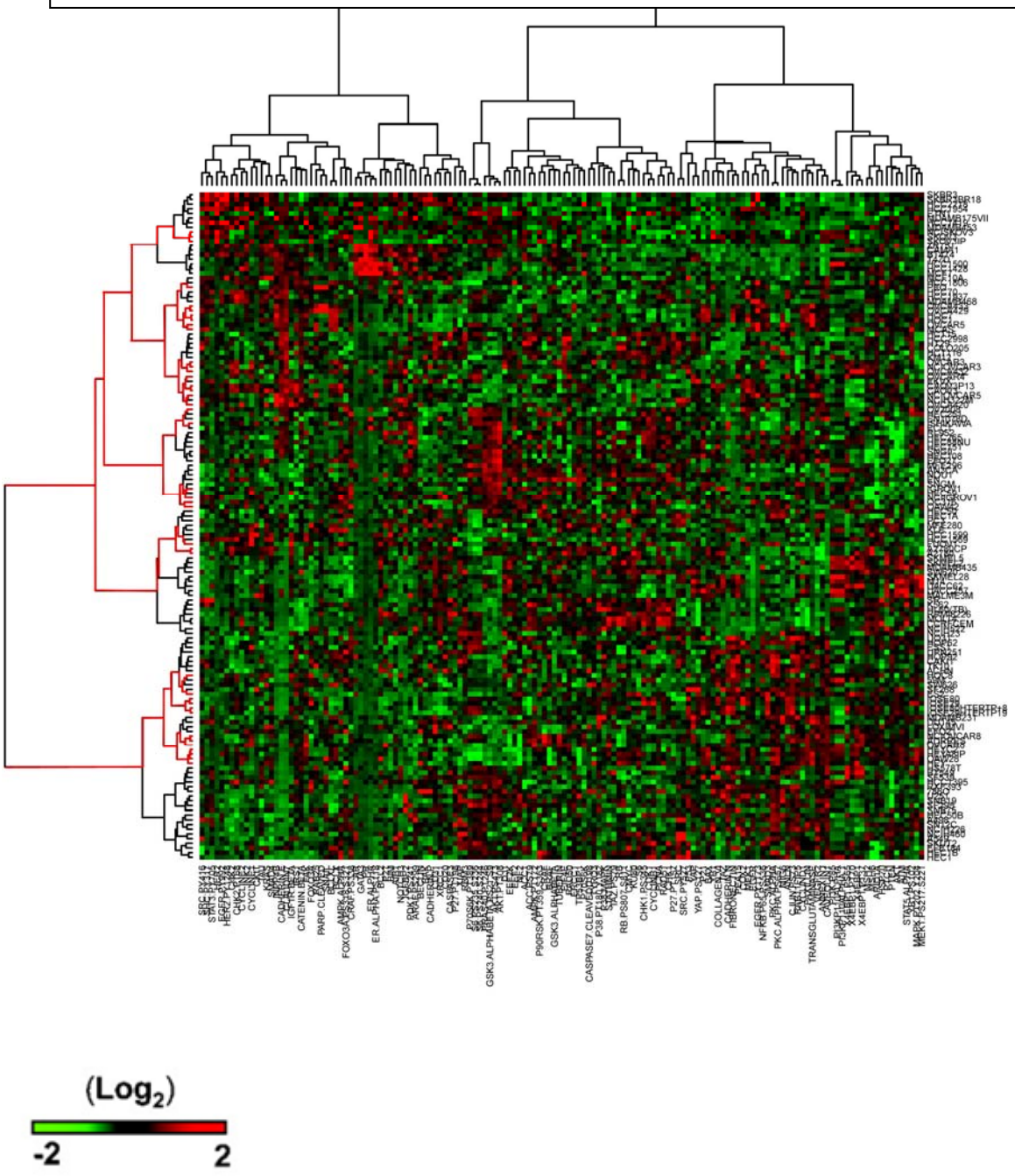

Figure 3: **Heatmap of Tumor samples.** Shown is the unsupervised hierarchical clustering of a subset of the ovarian samples. Indicated with the blue line are clustered samples of melanoma, lung or breast samples. The red lines indicate clusters of ovarian samples. The relative ordering of antibodies is listed in Table 1.

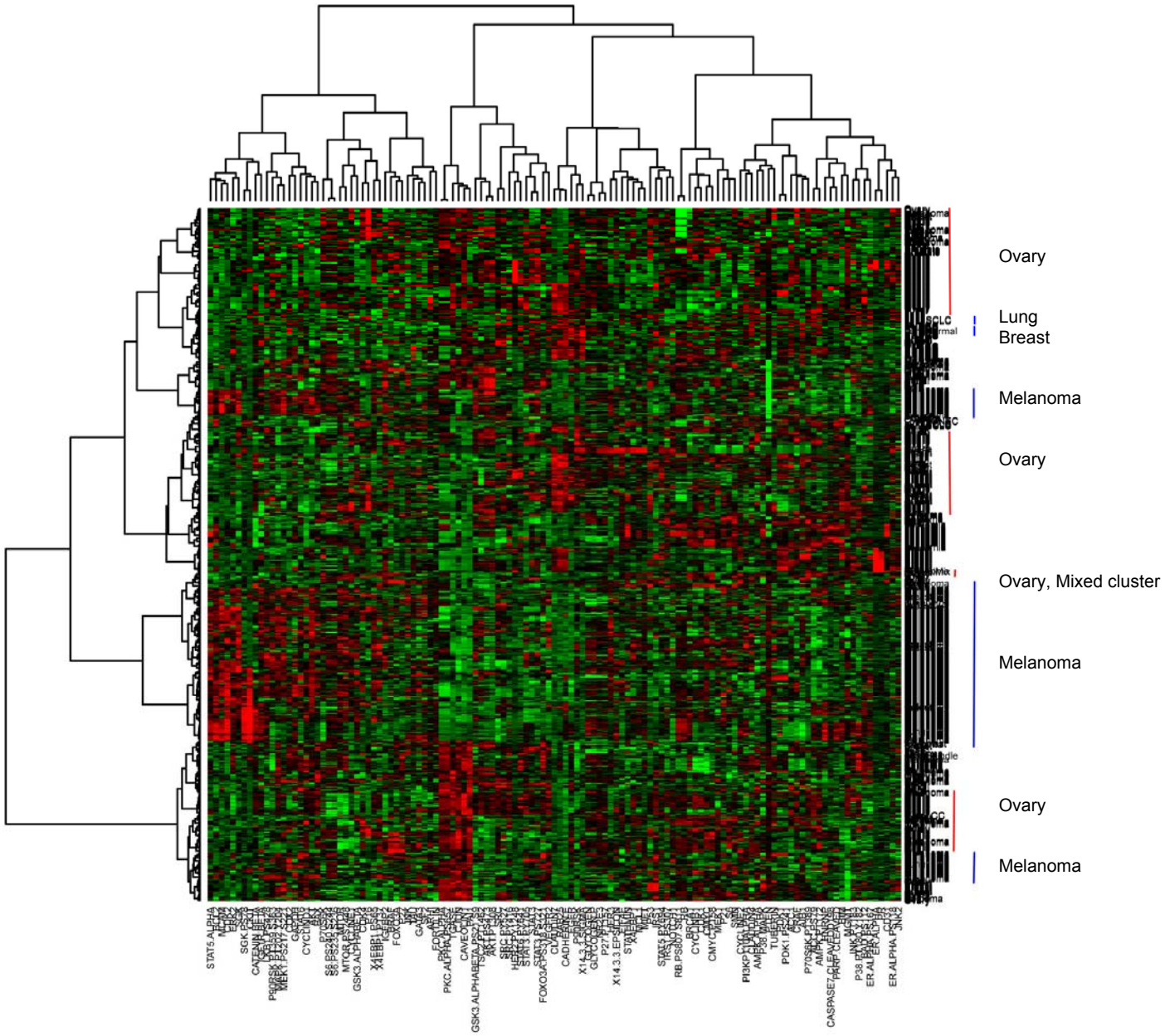

Table 1: List of antibodies tested, also INCLUDING a column indicating those that were validated for RPPA. The * indicates antibodies validated prior to this study.

Antibody name	Gene name	Validation Status	Position in Cell Lines	Position in tumor	Reference paper
14.3.3.EPSILON	14-3-3 protein, epsilon	Validated		73	60
14.3.3.SIGMA	14-3-3 protein, sigma	Not Valid		67	92
14-3-3 beta	14-3-3 protein, beta	Validated			60
14-3-3 zeta	14-3-3 protein, zeta	Validated			76
*4EBP1	(EIF4EBP1) Eukaryotic translation initiation factor 4E-binding protein 1	Validated	133	76	97
*4EBP1.P170	(EIF4EBP1) Eukaryotic translation initiation factor 4E-binding protein 1, phosphorylated	Use with caution	132		97
4EBP1.PS137	(EIF4EBP1) Eukaryotic translation initiation factor 4E-binding protein 1, phosphorylated	Use with caution	134		97
*4EBP1.PS65	(EIF4EBP1) Eukaryotic translation initiation factor 4E-binding protein 1, phosphorylated	Validated	131	30	97
*4EBP1.PT37	(EIF4EBP1) Eukaryotic translation initiation factor 4E-binding protein 1, phosphorylated	Validated		31	97
ACC.PS79	acetyl-CoA carboxylase 1	Validated	67	108	25
*ACC1	acetyl-CoA carboxylase 1	Validated	66	104	136
AIB1	(NCOA3) Steroid Receptor Coactivator Protein 32	Validated	40	106	7
*AKT	v-akt murine thymoma viral oncogene homolog 1	Validated	141	19	59
*AKT.PS473	v-akt murine thymoma viral oncogene homolog 1, phosphorylated	Validated	60	50	5
*AKT.PT308	v-akt murine thymoma viral oncogene homolog 1, phosphorylated	Validated	61	51	5
ALK	anaplastic lymphoma receptor tyrosine kinase	Not Valid			168
Alphaintegrin5	Alpha integrin5	Not Valid			4
AMPK.ALPHA	Protein Kinase, AMP-Activated, Alpha	Validated	29	98	125

*AMPK.PT172	activated under metabolic stress	Validated	68	109	125
ANLN	anillin, actin binding protein	Use with caution	119		11
ANNEXIN	(ANXA1) annexin A1	Validated	126		139
anti-IMP1	IMP1 inner mitochondrial membrane peptidase-like	no longer available			77
*AR	androgen receptor	Validated	32		143
ARAF.PS299	v-raf murine sarcoma 3611 viral oncogene homolog	Validated	44		86
ARHI	(DIRAS3) GTP-Binding RAS-Like protein	Use with caution		40	93
ARID1A	AT rich interactive domain 1A (SWI-like)	Use with caution	137		160
ATM	ataxia telangiectasia mutated	Not Valid	142		29
B-ACTIN	B-ACTIN	Use with caution	45		71
BAD	BCL2-Associated Agonist Of Cell Death	Validated			95
BAD.PS112	BCL2-Associated Agonist Of Cell Death, phosphorylated	Use with caution		117	57
BAK	BCL2-antagonist/killer 1	Validated	103		70
BAX	BCL2-Associated X Protein	Validated		20	124
*BCL2	B-cell CLL/lymphoma 2	Validated	37	2	19
BCLX	(BCL2L1) BCL2 like protein 1	Validated	28		91
BCLX1	(BCL2L1) BCL2 like protein 1	Validated	27		91
*BIM	(BCL2-like protein 11) bcl-2 interacting protein Bim	Validated	39	113	164
BRAF	v-raf murine sarcoma viral oncogene homolog B1	Validated	71	33	37
BRCA1	breast cancer 1, early onset	Not Valid		86	129
Ca19.9	carbohydrate antigen 19-9	Not Valid			26
CADHERIN P	placental cadherin	Validated	48		119
*CADHERIN.E	epithelial cadherin	Validated	16	64	36
*CADHERINN	neuronal cadherin	Validated	107		147
CASPASE3	caspase 3, apoptosis-related cysteine peptidase	Validated	51		9
CASPASE7.CLEAVEDD198	caspase 7, apoptosis-related cysteine peptidase	Validated	79	111	103

*CATENIN.BETA	catenin (cadherin-associated protein), beta 1	Validated	21	9	36
*CAVEOLIN1	caveolin 1, caveolae protein	Validated	127	46	159
CD20	B-lymphocyte antigen CD20	Use with caution	50		107
*CD31	(PECAM1)platelet/endothelial cell adhesion molecule 1	Validated	47	121	128
CDK1	cyclin-dependent kinase 1	Validated	91	88	56
CDK2	cyclin-dependent kinase 12	use with caution		4	141
CDK4	cyclin-dependent kinase 14	Not Valid		28	141
CHK1	checkpoint kinase 1	Validated	95		15
CHK1.P168	checkpoint kinase 1, phosphorylated	Use with caution	8		15
CHK1.PS345	checkpoint kinase 1, phosphorylated	Validated	90		15
CHK2	checkpoint kinase 2	Validated	7		15
CJUN	jun proto-oncogene	Not Valid		45	34
CJUN.PS73	jun proto-oncogene, phosphorylated	Not Valid	120		34
*CKIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	Validated	12	8	115
CLAUDIN4	claudin 4	Use with caution		97	1
CLAUDIN7	claudin 7	Validated	18	62	144
c-Met	met proto-oncogene (hepatocyte growth factor receptor)	Validated			131
c-Metp1230	met proto-oncogene (hepatocyte growth factor receptor),phosphorylated	Validated			131
CMYC	c-myc myelocytomatosis viral oncogene homolog	Validated	87	89	65
CMYC.PT58	c-myc myelocytomatosis viral oncogene homolog, phosphorylated	Not Valid		90	66
*CollagenVI	collagen, type VI, alpha 1	Validated	105		137
COMT	catechol-O-methyltransferase	Validated			84

COX2	(PTGS2)aglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	Validated	110	15	46
CRAF	(RAF1)v-raf-1 murine leukemia viral oncogene homolog 1	Validated	70	105	117
CRAF.PS338	(RAF1)v-raf-1 murine leukemia viral oncogene homolog 1, phosphorylated	Not Valid	31		117
*CYCLINB1	G2/Mitotic-Specific Cyclin B12	Validated	92	87	165
*CYCLIND1	G1/S-specific cyclin -D1	Validated	122	18	13
*CYCLINE1	cyclin E1 / G1/S-specific cyclin -E1 / cyclin Es / cyclin Et	Validated	11	26	20
CYCLINE2	cyclin E2 / G1/S-specific cyclin -E2	Validated	9	95	20
CYCLING1	cyclin G1	Validated			48
DJ1	(PARK7)parkinson protein 7	Validated	62		83
EEF2	elongation factor 2	Validated	64		88
EEF2K	elongation factor 2 kinase	Validated	63		8
*EGFR	epidermal growth factor receptor	Validated	112	65	114
*EGFR. PY992	epidermal growth factor receptor, phosphorylated	Validated	5		114
EGFR.Y1173	epidermal growth factor receptor, phosphorylated	Validated	113		114
*EIF4E	eukaryotic translation initiation factor 4E	Validated	74	74	74
EIG121		Use with caution			39
*ER.ALPHA	estrogen receptor	Validated	35	119	121
ER.ALPHA p118		Validated			121
*ER.ALPHA.	estrogen receptor	Validated		118	121
ER.ALPHA.PS167	estrogen receptor, phosphorylated	Validated	36	118	121
ERCC1		Validated	76		35
ERK2	Extracellular Signal Regulated Kinase 2	Use with caution		5	87
FABP4	fatty acid binding protein 4, adipocyte	Use with caution			104
FAK (BD)	(PTK2)protein tyrosine kinase 2	Not Valid	22		153

FAK (CST)	(PTK2)protein tyrosine kinase 2	Use with caution	46		153
FGFR1	fibroblast growth factor receptor 1	Not Valid			33
FIBRONECTIN	FIBRONECTIN 1	Validated	108		162
*FORTILIN	(TPT1) tumor protein, translationally-controlled 1	Validated		41	50
FOXO3A	forkhead box O3	Validated	23	34	45
FOXO3A.PS318.S321	forkhead box O3 , phosphorylated	Validated	30	60	45
GAPDH	glyceraldehyde-3-phosphate dehydrogenase	Not Valid		16	
*GATA3	GATA binding protein 3	Validated	33	38	157
GLYCOGEN	(PYGL)glycogen phosphorylase	Use with caution		68	44
GLYCOGEN.P	glycogen phosphorylase, phosphorylated	Use with caution		69	44
*GSK3.ALPHABETA	glycogen synthase kinase 3	Validated	72	27	28
*GSK3.ALPHABETA.PS21.S9	glycogen synthase kinase 3, phosphorylated	Validated	59	48	28
hCTR1	(SLC31A1)solute carrier family 31 (copper transporters), member 1	no longer available			62
HER2	(ERBB2)v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	Validated	4		123
*HER2.PY1248	(ERBB2)v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)	Validated	6	55	123
HER3	(ERBB3)v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	Validated		72	142
Heregulin	(NRG1)neuregulin 1	Validated			23
HMGA2	high mobility group AT-hook 2	Use with caution			99
HNRNP	hnRNP core protein A1	Use with caution		110	85
HSP27	heat shock 27kDa protein	Validated			163
HSP70	heat shock 70kDa protein	Use with caution	138		52

IGF1R.BETA	insulin-like growth factor 1 receptor	Validated	19	10	64
*IGFBP2	insulin-like growth factor binding protein 2	Validated	42	32	156
IMP-1 E20	(IGFBP1)insulin-like growth factor 2 mRNA binding protein 1	Not Valid			24
INPP4B	inositol polyphosphate-4-phosphatase, type II, 105kDa	Validated	17		61
IRS1	insulin receptor substrate 1	Validated	20	80	38
IRS1.PS307	insulin receptor substrate 1, phosphorylated	Not Valid		82	38
ITGAV	integrin, alpha V, vitronection	no longer available			73
JAB1	(SOCS1)suppressor of cytokine signaling 1	no longer available			63
JNK	c-JUN N-terminal kinase 1	Validated	10	36	101
JNK.PT183	c-JUN N-terminal kinase, phosphorylated	Not Valid		115	102
*JNK2	c-JUN N-terminal kinase 2	Validated			53
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	Not Valid	14		112
KU80	(PRKDC) protein kinase, DNA-activated, catalytic polypeptide	Use with caution	88		55
LKB1.PS428	(SKT11)serine/threonine kinase 11	Not Valid		11	125
LRP	low density lipoprotein receptor-related protein 1	no longer available			150
*MAPK.PT202.Y204	mitogen-activated protein kinase 1	Validated	145	13	158
MCAM	melanoma cell adhesion molecule	Validated		3	3
MCL1	myeloid cell leukemia sequence 1 (BCL2-related)	Not Valid		77	2
MDR1	(ABCB1)ATP-binding cassette, sub-family B (MDR/TAP), member 1	Not Valid			133
*MEK1	(MAP2K)Mitogen-activated protein kinase kinase	Validated	111	91	81
MEK1.PS217.S221	Mitogen-activated protein kinase kinase, phosphorylated	Validated	146	14	81

MGMT	O-6-methylguanine-DNA methyltransferase	Not Valid		114	17
MIFT	macrophage migration inhibitory factor (glycosylation-inhibiting factor)	Use with caution		78	79
MIG6	(ERRFI1)ERBB receptor feedback inhibitor 1	Validated	118		111
MSH2	DNA mismatch repair protein Msh2	Validated	135		130
MSH6	DNA mismatch repair protein Msh6	Validated	136		58
MTOR	mechanistic target of rapamycin (serine/threonine kinase)	Not Valid		24	96
MTOR.PS2448	mTOR, phosphorylated	Not Valid		25	49
NF2	neurofibromin 2	Validated	65		135
NFKB.PS536	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	Validated	114		21
NOTCH1	NOTCH1	Validated		83	127
NOTCH1 Cleaved	NOTCH1, cleaved	Not Valid			127
NOTCH3	NOTCH3	Validated	41		120
NR2E3	nuclear receptor subfamily 2, group E, member 3	Validated		70	122
P16	Cyclin-dependent kinase inhibitor 2A	Not Valid		29	82
P21	cyclin-dependent kinase inhibitor 1	Validated	102	92	90
P27	Cyclin-dependent kinase inhibitor 1B	Validated	38	35	113
P27.PT157	Cyclin-dependent kinase inhibitor 1B, phosphorylated	Not Valid	96		113
P27.PT157	Cyclin-dependent kinase inhibitor 1B, phosphorylated	Validated	52	71	113
*P38.MAPK	P38 mitogen-activated protein kinases	Validated	82	99	134
P38.PT180.Y182	P38 mitogen-activated protein kinases, phosphorylated	Validated	81	116	134
*P53	tumor protein p53	Validated	99	79	42
*P70S6K	ribosomal protein S6 kinase	Validated	78	21	67
*P70S6K.PT389	ribosomal protein S6 kinase, phosphorylated	Validated	55	107	67

P90RSK	p90 Ribosomal s6 kinase	Validated	69	66	138
P90RSK.PT359.S363	p90 Ribosomal s6 kinase, phosphorylated	Not Valid		12	138
PAI1	Plasminogen activator inhibitor-1	Use with caution		47	80
PARP.CLEAVED	Poly (ADP-ribose) polymerase	Validated	25	112	47
PAX2	paired box 2	Not Valid			148
PAXILLIN	(PXN) Paxillin	Validated	123		108
PCNA	Proliferating cell nuclear antigen	Validated	93		146
*PDK1	3-phosphoinositide dependent protein kinase-1	Use with caution		102	89
*PDK1.PS241	3-phosphoinositide dependent protein kinase-1, phosphorylated	Validated	43	103	89
PEA15	phosphoprotein enriched in astrocytes 15	Validated	109		16
PEA15, p	phosphoprotein enriched in astrocytes 15, phosphorylated	Validated			16
PI3K P85	phosphoinositide 3-kinase, p85 subunit	Validated	128		59
PI3KP110ALPHA	phosphoinositide 3-kinase, p110 subunit	Validated	129	96	59
PI3KP110ALPHA1	phosphoinositide 3-kinase, p110 subunit	Use with caution	130		59
*PKC.ALPHA	protein kinase C	Validated	116	42	105
*PKC.ALPHA.PS657	protein kinase C, phosphorylation	Validated	117	43	105
PR	progesteron receptor	Validated	34	120	132
PRAS40.P1246	(AKT1S1)AKT1 substrate 1 (proline-rich)	Validated	58		98
PTCH	Patched 1	Validated	139		126
*PTEN	phosphatase and tensin homolog	Validated	140	100	59
PTPN12A	protein tyrosine phosphatase, non-receptor type 12	Not Valid			152
RAB11.FIP5	RAB11A, member RAS oncogene family	Use with caution	121		69
*RAB25	RAB25, member RAS oncogene family	Validated	24	63	31
RAD50	DNA Repair Protein RAD50	Validated	75		155
RAD51	DNA Repair Protein RAD51	Use with caution	94		145

*RB	retinoblastoma 1	Validated	85	85	109
*RB.PS807.S811	retinoblastoma 1, phosphorylation	Validated	86	84	110
RBM3	RNA binding motif (RNP1, RRM) protein 3	Use with caution	54		41
REST	RE1-silencing transcription factor	Not Valid			51
RSK	(RPS6KA3) ribosomal protein S6 kinase, 90kDa, polypeptide 3	Use with caution			22
RSKpT359/S363	(RPS6KA3) ribosomal protein S6 kinase, 90kDa, polypeptide 3, phosphorylated	Not Valid			22
S6	ribosomal protein S6	Validated	89	93	94
*S6.PS235.S236	ribosomal protein S6, phosphorylation	Validated	56	23	94
*S6.PS240.S244	ribosomal protein S6, phosphorylation	Validated	57	22	94
SF2	alternative splicing factor/splicing factor 2	Validated		39	72
SGK	serum/glucocorticoid regulated kinase 1	Use with caution		6	32
SGK.PS78	serum/glucocorticoid regulated kinase 1, phosphorylation	Use with caution		7	32
SMA	smooth muscle actin	Not Valid			75
SMAD3	SMAD family member 3	Validated	115		116
SMAD3.PS423-425	SMAD family member 3, phosphorylated	Not Valid			116
SMAD4	SMAD family member 4	Validated	15		43
SMAD5.P	SMAD family member 5, phosphorylated	no longer available			78
SMN	survival motor neuron	Use with caution		94	154
SNAIL	snail homolog 1	Validated	26		30
*SRC	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog	Validated	97	52	30
SRC.PY416	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog, phosphorylated	Validated	2	54	30
*SRC.PY527	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog, phosphorylated	Validated	1	53	30

SRC.PY527	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog, phosphorylated	Validated	98		30
STAT3	signal transducer and activator of transcription 3	Not Valid		58	14
STAT3.PS727	signal transducer and activator of transcription 3, phosphorylated	Not Valid		59	14
*STAT3.PY705	signal transducer and activator of transcription 3, phosphorylated	Validated	3	57	14
*STAT5.ALPHA	signal transducer and activator of transcription 5	Validated	143	1	68
STAT5.PY694	signal transducer and activator of transcription 5, phosphorylated	Not Valid		81	68
STAT6	signal transducer and activator of transcription 6	Validated		17	149
STAT6.PY641	signal transducer and activator of transcription 6, phosphorylated	Not Valid		56	149
*STATHMIN	Stathmin 1	Validated	83	75	10
Survivin	(BIRC5)baculoviral IAP repeat containing 5	Not Valid			165
TAU	(MAPT) microtubule-associated protein tau splice variant	Validated	13	37	54
*TAZ	tafazzin	Validated	106		166
TAZ.PS79	tafazzin, phosphorylated	Use with caution	84		166
*TERT	telomerase reverse transcriptase	no longer available			151
TGASE	Epidermal Transglutaminase	Use with caution		44	27
TGFBR2	transforming growth factor, beta receptor	Not Valid			6
Topo II	topoisomerase II	Use with caution			161
TP53BP	p53 binding protein	Validated	77		118
TRANSGLUTAMINASE	(TGM1)transglutaminase 1 (K polypeptide epidermal type I, protein-glutamine-gamma-glutamyltransferase)	Validated	124		27
TSC2	tuberous sclerosis 2	Validated			59
TSC2.PT1462	tuberous sclerosis 2, phosphorylated	Use with caution		49	59

TUBERIN	(TSC2) tuberous sclerosis 2	Validated	73	101	100
TYRO3	Tyrosine-protein kinase receptor 3	Use with caution	80		167
*VEGFR2	(KDR) vascular endothelial growth factor receptor 2	Validated	125	61	106
VIM	Vimentin	Validated			12
XIAP	X-linked inhibitor of apoptosis	Validated	53		9
XRCC1	X-ray repair complementing defective repair	Validated	49		140
YAP	Yes-associated protein 1	Validated	100		166
*YAP.PS127	Yes-associated protein 1, phosphorylated	Validated	101		166
*YB1	Y-box protein 1	no longer available	104		18
YB1.PS102	Y-box protein 1, phosphorylated	Validated	144		18
YKL40	(CH3IL1)chitinase 3-like 1	Not Valid			40

Table 2: List of Cell Line Names: Below are the names of the cell lines and their position in Figure 2.

#	Cell Line	#	Cell Line	#	Cell Line	#	Cell Line
1	SKBR3	41	EKVX	81	MDA-MB-435	121	HEY A8 IP
2	SKBR3 BR18	42	CAOV3	82	SW620	122	OAW28
3	HCC2218	43	CAOV3	83	SK-Mel28	123	HEY
4	HCC1954	44	OVCAR5 (NCI)	84	M14	124	HS578T
5	ETN1	45	NCI H322M	85	UACC62	125	BT549
6	MDA-MB-175Viii	46	OVCA420	86	UACC257	126	SF539
7	HCC1419	47	OV2008	87	MALME-3M	127	HCC1395
8	MDA-MB-453	48	HEC25	88	SR	128	RXF393
9	SKOV3 (NCI-60)	49	EN1078D	89	K562	129	786-o
10	SKOV3	50	ISHIKAWA	90	HL-60	130	U251
11	SKOV3 ip	51	ECC1	91	RPMI-8226	131	SNB19
12	ZR75-1	52	RL95-2	92	MOLT4	132	SF295
13	CAMA1	53	HEC265	93	CCRF-CEM	133	SNB75
14	BT474	54	HEC88NU	94	NCI-H522	134	HEC50B
15	T47D	55	HEC151	95	NCI H23	135	A498
16	HCC1500	56	SNGII	96	UO31	136	SNI2C
17	HCC1428	57	HEC108	97	HOP62	137	NCI-H226
18	MCF7	58	EFO27	98	ESS1	138	NCI-H460
19	MCF10A	59	MFE-296	99	UPN251	139	A549
20	HCC1806	60	AN3CA	100	HOP92	140	SK-UT-2
21	PEO	61	NOU1	101	CAKI	141	EFE-184
22	HCC70	62	EN	102	TK10	142	HEC1B
23	HCC1937	63	SNGM	103	ACHN	143	HEC1
24	MDA-MB-468	64	IGROV1	104	HOC8		
25	OVCA433	65	HEC59	105	59M		
26	OVCA429	66	IGROV1 (NCI)	106	SW626		
27	HOC7	67	OC316	107	SE268		
28	HOC1	68	OAW42	108	ES2		
29	OVCAR5	69	HEC50	109	IOSE80		
30	MCAS	70	HEC1A	110	IOSE29		
31	HCT15	71	PC3	111	IOSE80		
32	HCC2998	72	MFE280	112	IOSE29		
33	H129	73	KLE	113	MDA-MB-231		
34	COLO205	74	HEC1599	114	DU145		
35	HCT116	75	HCC1569	115	LOXMVI		
36	KM12	76	FUOV1	116	EFO-21		
37	OVCAR3	77	A2780 CP	117	OVCAR8 (NCI)		
38	OVCAR3(NCI)	78	A2780	118	ADR/RES		
39	OVCA432	79	SK-MEL-5	119	OVCAR8		
40	OVCAR4	80	SK-MEL2	120	HEY C2		

Table 3: Position of antibodies when tumor samples were clustered.
Data from Table 1 was resorted to display the order of the antibodies used in Figure 2. Antibody names in green are validated, orange are "use with caution" and red are not valid.

Position in tumor	Antibody name	Position in tumor	Antibody name	Position in tumor	Antibody name
1	STAT5.ALPHA	42	PKC.ALPHA	84	RB.PS807.S811
2	BCL2	43	PKC.ALPHA.PS657	85	RB
3	MCAM	44	TGASE	86	BRCA1
4	CDK2	45	CJUN	87	CYCLINB1
5	ERK2	46	CAVEOLIN1	88	CDK1
6	SGK	47	PAI1	89	CMYC
7	SGK.PS78	48	GSK3.ALPHABETA.PS21.S9	90	CMYC.PT58
8	CKIT	49	TSC2.PT1462	91	MEK1
9	CATENIN.BETA	50	AKT.PS473	92	P21
10	IGF1R.BETA	51	AKT.PT308	93	S6
11	LKB1.PS428	52	SRC	94	SMN
12	P90RSK.PT359.S363	53	SRC.PY527	95	CYCLINE2
13	MAPK.PT202.Y204	54	SRC.PY416	96	PI3KP110ALPHA
14	MEK1.PS217.S221	55	HER2.PY1248	97	CLAUDIN4
15	COX2	56	STAT6.PY641	98	AMPK.ALPHA
16	GAPDH	57	STAT3.PY705	99	P38.MAPK
17	STAT6	58	STAT3	100	PTEN
18	CYCLIND1	59	STAT3.PS727	101	TUBERIN
19	AKT	60	FOXO3A.PS318.S321	102	PDK1
20	BAX	61	VEGFR2	103	PDK1.PS241
21	P70S6K	62	CLAUDIN7	104	ACC1
22	S6.PS240.S244	63	RAB25	105	CRAF
23	S6.PS235.S236	64	CADHERIN.E	106	AIB1
24	MTOR	65	EGFR	107	P70S6K.PT389
25	MTOR.PS2448	66	P90RSK	108	ACC.PS79
26	CYCLINE1	67	14.3.3.SIGMA	109	AMPK.PT172
27	GSK3.ALPHABETA	68	GLYCOGEN	110	HNRNP
28	CDK4	69	GLYCOGEN.P	111	CASPASE7.CLEAVEDD198
29	P16	70	NR2E3	112	PARP.CLEAVED
30	4EBP1.PS65	71	P27.PT157	113	BIM
31	4EBP1.PT37	72	HER3	114	MGMT
32	IGFBP2	73	14.3.3.EPSILON	115	JNK.PT183
33	BRAF	74	EIF4E	116	P38.PT180.Y182
34	FOXO3A	75	STATHMIN	117	BAD.PS112
35	P27	76	4EBP1	118	ER.ALPHA.
36	JNK	77	MCL1	118	ER.ALPHA.PS167
37	TAU	78	MIFT	119	ER.ALPHA
38	GATA3	79	P53	120	PR
39	SF2	80	IRS1	121	CD31
40	ARHI	81	STAT5.PY694		
41	FORTILIN	82	IRS1.PS307		
		83	NOTCH1		

Table 4: Assignment of cell lines to early and late stage.
Shown in red are cell lines that could not be classified based on RPPA data alone.

Cell Line Name	Group I					Group II
	Advanced Stage					Early Stage
	1	2	3	4	5	Early Stage
59M						
A1847						
A2780						
A2780CP						
CAOV-3						
CAOV-4						
CAOV3 p10						
DOV 13						
DOV13mHA_AKT2DD						
DOV13mHAAKT1AAA						
DOV13p110*						
DOV13pcDNA3 p+9						
EFO21						
EFO27						
ES-2						
ES-2						
FUOV1						
HEY						
HEY A8						
HEY A8 -bcl2						
HEYC2 p16						
HEYC2-bcl2 p30						
HEYC2+bcl2 p30						
HOC1						
HOC7						
Hs 38.T						
IGROV1						
IOSE 29						
IOSE 80						
NIH:OVCAR						
OAW42						
OC316						
OCC1 p21						
OV-90						
OVCA 420						
OVCA 429						
OVCA 432						
OVCA433 p75						
OVCAR 3						
OVCAR 8						
OVCAR3						
OVCAR4						
OVCAR5						

OVCAR8						
PA-1						
PEO1						
(NCI-60) SKOV3						
SKOV 3						
SKOV 3 IP						
SW 626						
TOV-21G						
UPN251						